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Synthesis of Nonlinear Optical Peptides

by
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Canyon, Texas 79016
for the
Research Department*

DECEMBER 1992

NAVAL AIR WARFARE CENTER WEAPONS DIVISION
CHINA LAKE, CA 93555-6001



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Naval Air Warfare Center Weapons Division

FOREWORD

Second-order nonlinear optical polymers are being developed for high speed optical signal processors, such as fiber-optic switches, modulators, and beam steering devices. The goal of this project was to prepare new polymers and films having improved optical figures of merit and thermal stability by taking advantage of the self-ordering properties of polypeptides. Our objective was to synthesize polypeptides containing pendent chromophores which would assemble into the β -sheet conformation while floating on a water surface. Multilayers of this floating monolayer would be built up into an optical waveguide by Langmuir-Blodgett processing. This was the third year that Professor Alfred Schram worked at China Lake on a U.S. Navy/American Society for Engineering Education (ASEE) Summer Faculty Fellowship. This technical paper describes his work from 1 Jun-7 Aug 1992.

This work was sponsored by the Office of Naval Research (S. Snyder, ONR 121), Contract N00014-91-W-22049, Program Element 61153N, Task Area R2206, and Work Unit 138584. This report has been reviewed for technical accuracy by Geoffrey A. Lindsay.

Approved by
R. L. DERR, *Head*
Research Department
11 December 1992

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13. ABSTRACT (Maximum 200 words)

Two dozen dye-conjugate peptides were synthesized in a 10-week period in an attempt to produce nonlinear optical polymers that self-assemble into β -sheets. These would then be processed into second-order nonlinear optical films by Langmuir-Blodgett deposition. Glutamate-chromophore conjugates gave soluble polymers, whereas lysine amides and imines of chromophores gave insoluble polymers. The soluble polymers will be characterized for composition and film-forming properties. Eight dipeptide-dye conjugates were synthesized for subsequent polymerization at the air-water interface of a Langmuir-Blodgett trough. The soluble polypeptide conjugates and dipeptides are available when time and funding permits continued investigation.

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Langmuir-Blodgett, Nonlinear optical polymers, Polypeptide, Conjugates

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Many of the chromophores used were synthesized by R. A. Henry (Naval Air Warfare Center Weapons Division (NAWCWPNS)). Useful suggestions, equipment, and chemical reagents were provided by G. A. Lindsay, J. M. Hoover, J. D. Stenger-Smith, and R. A. Henry (all of NAWCWPNS). R. A. Nissan (NAWCWPNS) provided the nuclear magnetic resonance spectra and D. Olshefski (University of California, San Diego) made peptides 602, 632, and 725. This investigation was sponsored by Dr. S. Snyder (Code 121, Office of Naval Research).

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INTRODUCTION

This is the third report on the synthesis of nonlinear optical polypeptide conjugates (References 1 and 2). Previous efforts lead to polypeptides with low solubilities, hampering the determination of physical properties and especially the fabrication of thin films. The preparation of a few polypeptide conjugates has been reported; for example, poly(L-glutamic acid) with photochromic ester side chains (References 3 through 6) or poly(L-lysine) with photochromic amide side chains (References 7 and 8). But these polypeptide conjugates also have low solubilities. In these preparations, esterification of the free γ -carboxyl groups of poly(L-glutamic acid) or amide formation of the free ϵ -amino groups of poly(L-lysine) was incomplete, leaving polar side chains which appear to reduce the solubility in organic solvents.

Since poly(γ -benzyl-L-glutamate) is soluble in organic solvents such as chloroform, poly(L-glutamate-dye) conjugates were synthesized with γ -benzyl ester functions rather than free carboxyl groups. As was expected, these polypeptides were more readily soluble in organic solvents. The poly(ϵ -amide or imine-L-lysine) conjugates had low solubilities. Dye conjugates of polymers of leucyllysine or alanyllysine also lacked adequate solubility for purification and film formation.

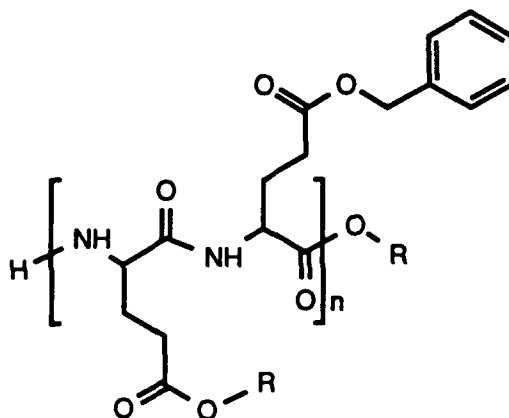
The compounds synthesized for this report are listed in the Experimental Section.

EXPERIMENTAL SECTION

(Excerpts from NAWCWPNS Laboratory Notebook 1423)

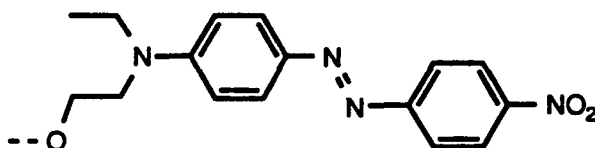
Homopolymer Derivatives

Poly(L-glutamates)

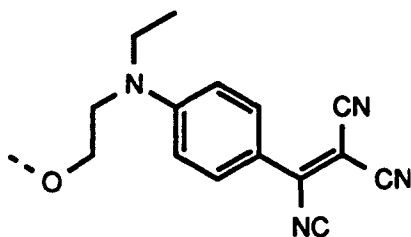


The preparation sequence included hydrolysis of poly(γ -benzyl-L-glutamate) followed by esterification with an appropriate dye in the presence of dicyclohexylcarbodiimide. Essentially, poly(γ -benzyl-L-glutamate) is dissolved in boiling dioxane; a two-fold excess of NaOH (based on ester groups) dissolved in the minimum amount of water is added; the mixture is refluxed for an hour, after which the dioxane and most of the generated benzyl alcohol are removed *in vacuo*. The residual gum is taken up in water, acidified with 5 N HCl, and filtered. After washing with water and alcohol, the polypeptide is dried. It can then be dissolved in the minimum amount of hot dimethylformamide, diluted with two volumes of dichloromethane, cooled to 5°, mixed with dicyclohexylcarbodiimide and a hydroxyl-containing dye, stirred at room temperature for 2 to 5 days, filtered, and evaporated to a small volume *in vacuo*. The residual thick liquid is dropped into vigorously stirred alcohol. After centrifugation, the solid residue is dissolved in a minimum amount of dichloromethane or chloroform, centrifuged to remove any insoluble material, and precipitated with alcohol or ether. The process is repeated until the washings are colorless.

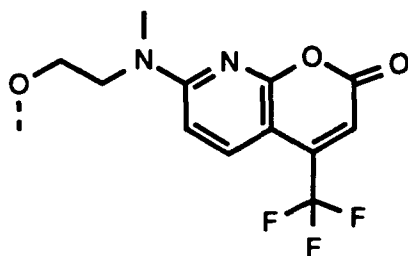
1423-21, 1423-48; R = 4-(4-nitrophenylazo)-N-ethyl, N-2-hydroxyethylaniline (disperse Red 1)



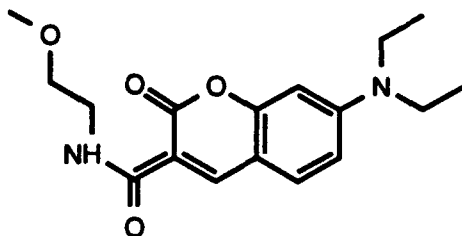
1423-64; R = 4-(1,2,2-tricyanovinyl)-N-ethyl, N-2-hydroxyethylaniline



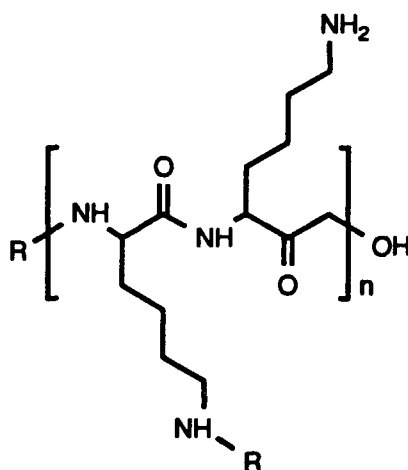
1423-67; R = 2 H-7-(2-hydroxyethyl)methylaminopyrido[3,2-b]-4-trifluoromethylbenzopyran-2-one



1423-78; R = 7-diethylamino-3-(N-2-hydroxyethyl)coumarine-carboxamide

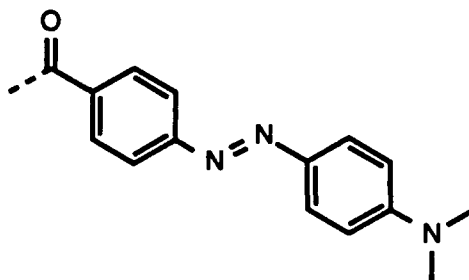


Poly(L-lysines)



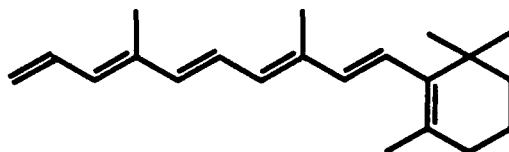
The amides were prepared by condensation between poly(L-lysine) and acidic dyes in the presence of a carbodiimide and 1-hydroxybenzotriazole. The imines were obtained by condensation between poly(L-lysine) and appropriate aldehydes.

1423-18, 1423-19, 1423-29; R = 4-(4-dimethylaminophenylazo)benzoyl



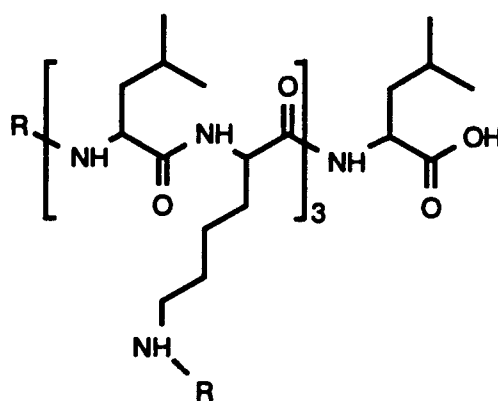
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1423-70; R = all *trans*-retinal

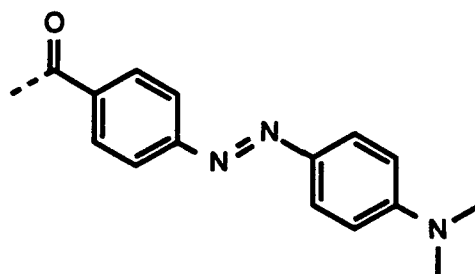


Copolypeptide Derivatives

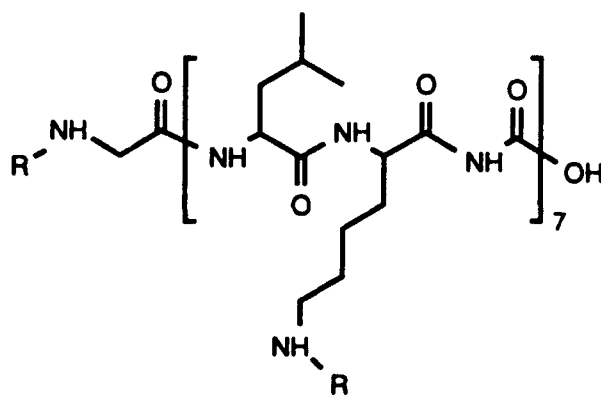
Peptide 602 derivative



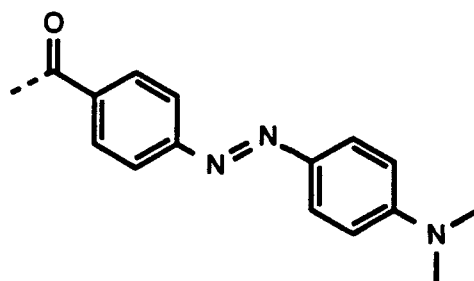
1423-33; R = 4-(4-dimethylaminophenylazo)benzoyl



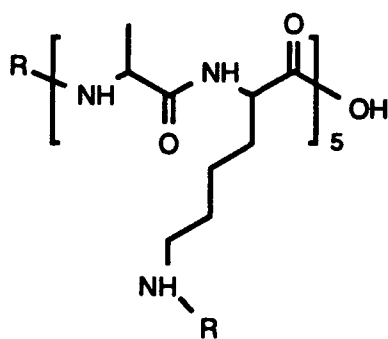
Peptide 631 derivative



1423-35; R = 4-(4-dimethylaminophenylazo)benzoyl

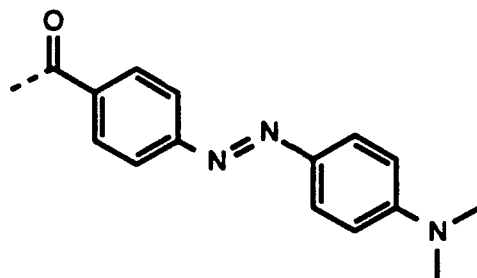


Peptide 725 derivatives

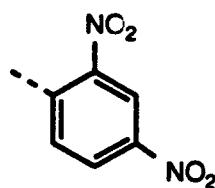


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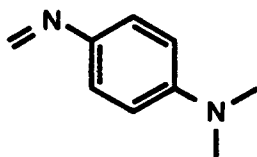
1423-50; R = 4-(4-dimethylaminophenylazo)benzoyl



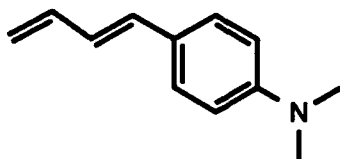
1423-57; R = 2,4-dinitrophenyl



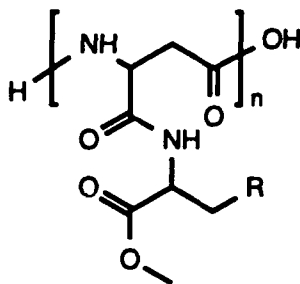
1423-71; R = 4-dimethylaminophenylazo



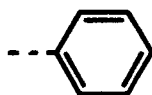
1423-72; R = 4-dimethylaminocinnamal



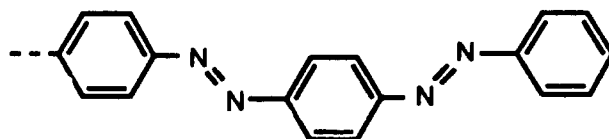
Poly(L-aspartylphenylalanine) derivatives



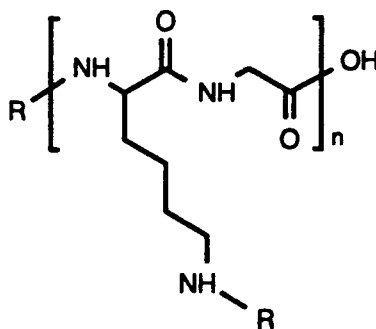
1423-26; R = phenyl



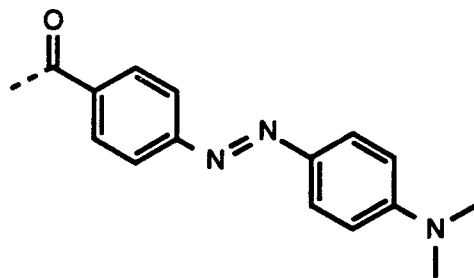
1423-61; R = 4-(4-phenylazo)phenylazophenyl



Poly(L-lysylglycine) derivative



1423-58; R = 4-(4-dimethylaminophenylazo)benzoyl

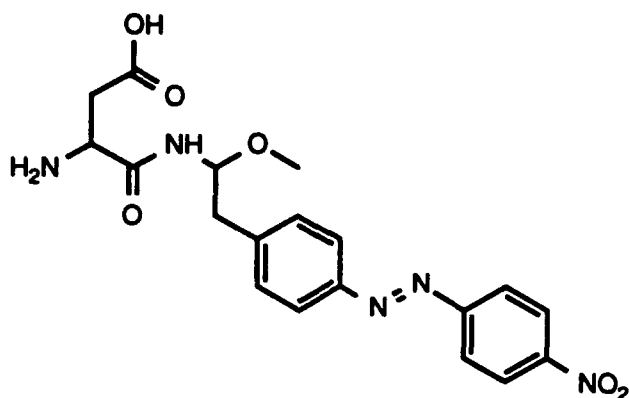


Dipeptides

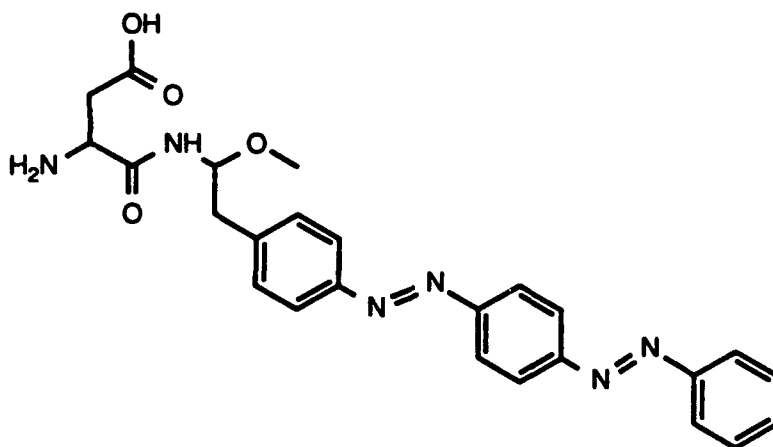
Dipeptides of suitable amino acids were synthesized according to either of the two sequences: (1) two protected amino acids were bonded and the still-protected dipeptide was derivatized with a chromophore; (2) a protected amino acid was derivatized with a chromophore and bonded to another amino acid. The dipeptides were synthesized as precursors to copolypeptides.

Aspartame derivatives

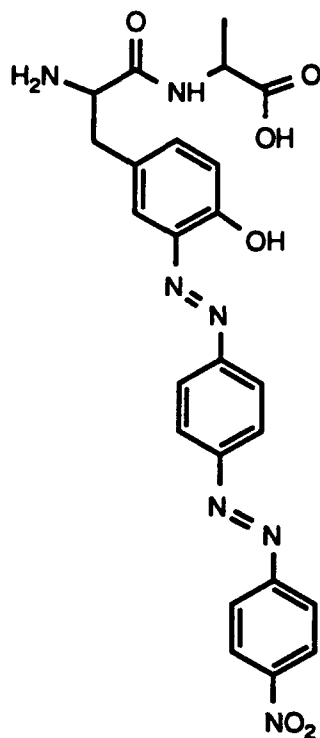
1423-04, 1423-14; aspartyl-4-(4-nitrophenylazo)phenylalanine methyl ester;
m.p. is 169-170°



1423-53; aspartyl-4-(4-phenylazo)phenylazophenylalanine methyl ester;
m.p. 114° (d)

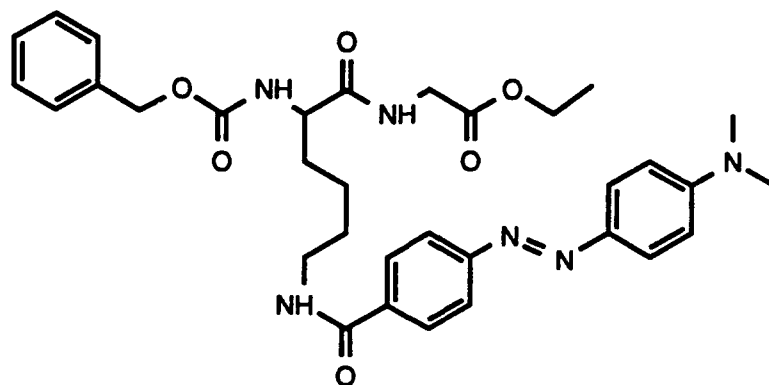


1423-34; 3-(4-nitrophenylazo)phenylazotyrosylalanine; (decomposes above 125°)



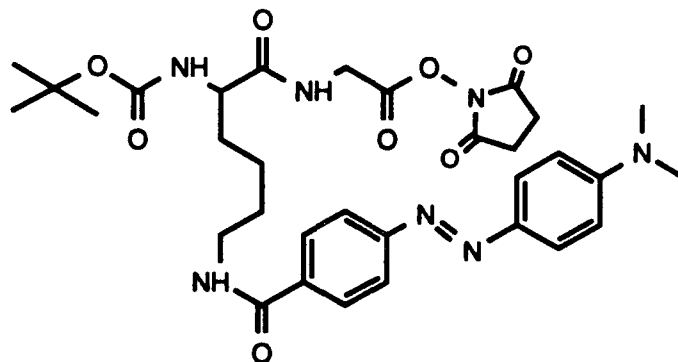
L-Lysylglycine derivatives

1423-52; α -benzyloxycarbonyl- ϵ -4-(4-dimethylaminophenylazo)benzoyllysylglycine ethyl ester

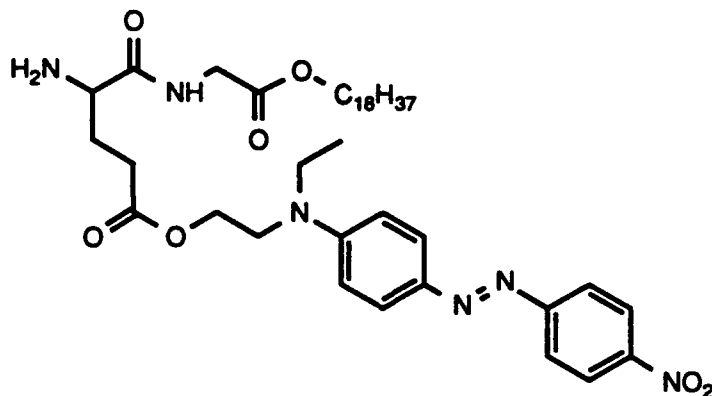


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1423-54; α -t-butyloxycarbonyl- ϵ -4-(4-dimethylaminophenylazo)benzoyllysine N-hydroxysuccinimide ester; m.p.; is 206-209°

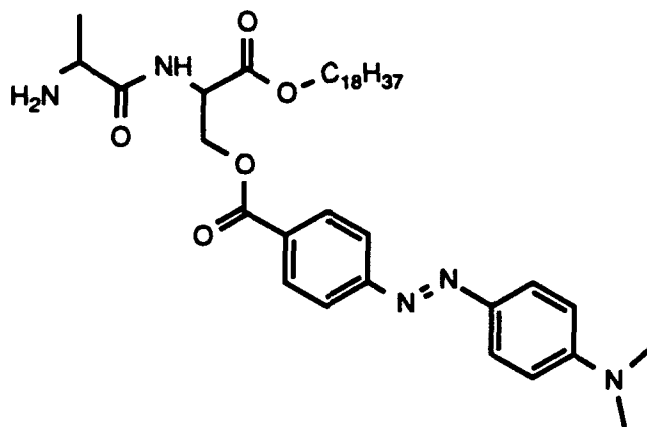


1423-62; γ -[4-(4-nitrophenylazo)-N-ethyl, N-2-hydroxyethylanilide]glutamylglycine octadecyl ester

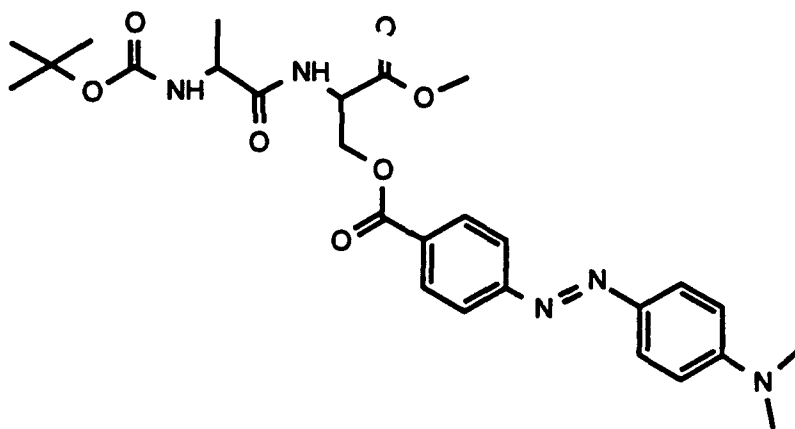


L-Alanyl-L-serine derivatives

1423-73; alanyl-O-4-(4-dimethylaminophenylazo)benzoylserine octadecyl ester



1423-79; t-butyloxycarbonylalanyl-O-4-(4-dimethylaminophenylazo)benzoylserine methyl ester



DISCUSSION

Polypeptide molecules spontaneously assume stable, highly organized conformations such as α -helices or β -sheets. Typically, the α -helices impart solubility, while the β -sheet conformation is associated with highly insoluble polypeptides. The β -sheet conformation is based on the antiparallel juxtaposition of stretched out polypeptide chains with the side chains of alternating amino acyl units located on the same side of the sheet (Reference 9). With side chains of alternating units made of a polar chromophore, the whole sheet would form a very thin film with the capability of strong second harmonic generation. The rigidity and stability of the beta-sheet conformation should also prevent or at least reduce randomness in orientation of the chromophores' dipole moments.

Poly(L-lysine) amides and imines of chromophores had very low solubilities in organic solvents. Since not all the side chains have been substituted, and the substitution is most probably random, second harmonic generation could be induced through poling during film formation. But the lack of solubility in volatile solvents hampers these processes.

Copolypeptides of alternating amino acyl and amino acyl-chromophore sequences should form polar Langmuir monolayers, since in the β -sheet conformation, the pendant chromophores should be parallel to each other (Reference 1). The lysyl side chains of oligopeptides of leucyllysine or alanyllysine sequences were coupled to chromophores, but in these preparations also, insolubility in volatile solvents makes film fabrication difficult.

Poly(γ -benzyl-L-glutamate) on the other hand is soluble in chloroform; however, if some of the side chains have a free carboxyl group, the peptide becomes insoluble in chloroform. Even in the case in which up to 85% of the side chains have an ester function (Reference 6), the solubility is very low.

To maintain solubility, poly(γ -benzyl-L-glutamate) was partially hydrolyzed, and the freed carboxyl groups were esterified to photochromic dyes. The products obtained in this fashion were highly colored, and still soluble in chloroform and in dichloromethane. The original γ -benzyl ester groups were most probably hydrolyzed at random, and thus the chromophores are also assumed to be located at random along the polypeptide backbone. The solubility suggests an α -helix conformation at least in solution. Therefore, poling should be necessary to align the chromophore during film fabrication.

Should the films be stable and exhibit substantial second harmonic generation, the synthesis offers a good alternative to the reported methods; furthermore, the starting poly(γ -benzyl-L-glutamate) is about five times cheaper than poly(glutamic acid).

CONCLUSIONS

Several γ -esters of poly(L-glutamic acid) were synthesized by replacing some of the benzyl esters of the starting material by dye esters. All were soluble in dichloromethane and in chloroform to yield highly colored solutions. Poling during evaporation of these solutions should provide thin films with parallel chromophore pendants.

Copolypeptides prepared from dipeptides, one unit of which has a chromophore, may provide both solubility and conformation stability. For example, poly(γ -benzyl-L-glutamate-alt- γ -dye-L-glutamate) should readily assume the β -sheet conformation for proper orientation in the solid state, and yet be soluble in chloroform, since all the side chains have ester functional groups. Other sequences (for instance, involving serine O-esters) may provide useful alternatives.

Poly(L-lysine amide or imine) conjugates were easily prepared, but lacked the needed solubilities. The solubility does not appear to depend on peptide size, since poly-(L-lysine) derivatives with the number of lysyl units varying from 3 (compound 1423-33) to 800 (compound 1423-18 and others) were all insoluble in chloroform.

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